that is shared with the membrane-bound precursor of epidermal growth factor (EGF). The domain consists of two, 40–50-amino-acid, cysteine-rich repeats of the EGF class, then five copies of a roughly 50-amino-acid (cysteine-poor) repeat which is characterized by the consensus sequence YWTD. This is followed by a third, cysteine-rich, EGF repeat (Fig. 1). When the EGF-precursor domain is deleted from the LDLR, the receptor can no longer bind LDL but it still binds lipoproteins that contain apoE¹⁰. The bound ligands enter the cell as normal, but they are not released in the endosome — instead, the receptor is degraded along with the ligand. *In vitro* binding studies have shown that the deleted receptor fails to release its ligand at acid pH, thereby explaining its failure to recycle¹⁰.

Although the EGF repeats each contain three disulphide bonds, they otherwise differ from the ligand-binding repeats. For example, an NMR structure of two adjacent EGF repeats from fibrillin reveals that, rather than being trapped in a cage, Ca²⁺ bridges the gap between repeats¹¹. The mechanism by which the EGF-precursor region of the LDLR facilitates dissociation of lipoproteins from the ligand-binding region is not known. But, at acid pH, the EGF region probably undergoes a conformational change that is mediated either by the dissociation of Ca²⁺ or by titration of the aspartic acids in the YWTD repeats.

The third important domain of the LDLR is the 50-amino-acid cytoplasmic tail, which contains the sequence NPxY (where x is any amino acid; Fig. 1). This sequence forms a reverse turn¹², and it clusters the receptor into coated pits, apparently by interacting with a clathrin-associated protein¹³. Phosphorylation of the tyrosine residue in NPxY is not required for coated-pit clustering — phenylalanine can substitute without effect¹³.

There are, to date, seven members of the LDLR family (Fig. 1). Although other proteins contain LDLR ligand-binding repeats or EGF repeats, these seven are the only proteins that contain both. All except the insect varieties also share the NPxY signature in the cytoplasmic tail. In the insect receptors, NPxY is replaced by a dileucine motif¹⁴, which can also mediate coated-pit clustering.

The behemoths of the family are the LDLR-related protein (LRP) and megalin/gp330. Megalin (4,660 amino acids) contains 36 ligand-binding repeats and eight EGF-precursor domains, the arrangement of which is almost completely conserved from nematodes to mammals¹⁵. Each member of the LDLR family binds many ligands, and the number of ligands bound seems to increase with the number of ligand-binding repeats. The champion is LRP, which has at least 20 known ligands ranging from lipoproteins (chylomicron remnants) and protease inhibitors (α_2 -macroglobulin) to plasminogen activators¹⁵. Each macromolecule probably binds to a unique combination of

ligand-binding repeats.

Members of the LDLR family can transfer large amounts of macromolecules into cells due to the combination of Ca²⁺-stabilized binding repeats, acid-regulated EGF-precursor regions and cytoplasmic internalization signals. For example, the vitellogenin receptor transports 1.5 g of protein into the chicken oocyte each day, as the single cell grows to the size of a grade AA jumbo egg over seven days. A mutation in this receptor causes the female-sterile 'restricted ovulator' phenotype, in which chicken oocytes do not grow to normal size¹⁶. A mutation in the *Drosophila* homologue of the vitellogenin receptor also produces a female-sterile phenotype, *yolkless*¹⁴.

Now that Fass *et al.*¹ have solved the structure of a single ligand-binding repeat, we need to know how the repeats are orientated with respect to each other and to the other domains. In fibrillin, where Ca²⁺ bridges two adjacent EGF repeats, the repeats are probably stacked in an extended fashion, perhaps in the form of a helix¹¹. And as the ligand-binding repeats of the LDLR are separated by short, 4–5-amino-acid sequences which do not allow for much flexibility, these repeats could also be stacked atop one another. The exception is a 12-residue spacer between repeats 4 and 5 which, in LDLRs from all known species, is conserved in length but not in sequence¹⁷. Does this spacer form a loop that allows the stacks of repeats to double back on one another? The answer will surely be forthcoming now that Fass *et al.* have taught us how to assemble, crystallize and appreciate a rigid, disulphide-bonded Ca²⁺ cage. □

Michael S. Brown, Joachim Herz and Joseph L. Goldstein are in the Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, Texas 75235, USA.

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Daedalus

Command performance

Some while ago Daedalus proposed the use of pulsed magnetic fields in psychotherapy. Unlike electro-shock therapy, they induce purely local currents in the brain. The technique now seems to be maturing. It is claimed that pulsed magnetic fields, applied to specific regions of the brain, can affect motor control or relieve depression. So Daedalus is now sharpening the selectivity of the method, and extending it to the nervous system as a whole.

A tightly shaped magnetic pulse will induce current in, and therefore fire, nerves in quite a small region of tissue. By itself, this might not be useful; even a narrow nerve trunk can carry thousands of individual fibres, each with a different destination. But Daedalus feels that each fibre must have its own 'resonant frequency', possibly quite broad, at which it will fire most effectively. It may also respond best to a specific shape of pulse. So if magnetic pulses of carefully adjusted frequency, amplitude and shape are aimed at a nerve trunk, they should trigger just one class of fibre (those to a specific muscle, say) without affecting the rest.

Magnetic pulsing could wonderfully improve muscular coordination and strength. Daedalus recalls an electrician who claims the world record for throwing the pliers. He touched a high-voltage terminal with them, and every muscle-fibre in his arm contracted at once, more forcefully than he could have managed by any act of will. So Daedalus is devising a magnetic-pulse machine to be placed round an athlete's neck. Without the pain and imprecision of electric stimulation, it will take over the spinal nerves leading to his arms and legs. A well-designed 'neuromagnetic program', firing the right nerves in the right sequence, would then let him run, jump or throw with ultimate power and accuracy. An Olympic committee would probably disallow these achievements. Even so, by training with the system, he could hone his own voluntary action to utter perfection.

Sensory nerves could also be triggered, or indeed inhibited. At present, implanted coils are used to block pain, for example from damaged joints. A magnetic inhibitor would be far less invasive, and could be turned on or adjusted in seconds. It could even abolish pain while leaving sensation untouched. As centralized medical services run down, it could become an ideal surgical aid. With a magnetic inhibitor, a scalpel, a mirror and a DIY manual, you could remove your own appendix.

David Jones